

FIRST-TRIMESTER GROWTH AND THE RISK OF LOW BIRTH WEIGHT

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AND JOHN E.E. FLEMING**ABSTRACT**

Background Previous studies have demonstrated a correlation between first-trimester size and birth weight. It is not known, however, whether low birth weight is related to first-trimester growth. We sought to determine whether the risk of low birth weight and birth weight that was low for gestational age is related to the size of the embryo or the fetus in the first trimester.

Methods From a data base of ultrasound records of more than 30,000 pregnancies, we identified women who had no important medical problems, a normal menstrual history, and a first-trimester ultrasound scan in which the crown-rump length of the embryo or fetus had been measured. We examined the relation between the outcome of 4229 pregnancies and the difference between the measured and the expected crown-rump length in the first trimester, expressed as equivalent days of growth.

Results A first-trimester crown-rump length that was two to six days smaller than expected was associated with an increased risk (as compared with a normal or slightly larger than expected crown-rump length) of a birth weight below 2500 g (relative risk, 1.8; 95 percent confidence interval, 1.3 to 2.4), a birth weight below 2500 g at term (relative risk, 2.3; 95 percent confidence interval, 1.4 to 3.8), a birth weight below the fifth percentile for gestational age (relative risk, 3.0; 95 percent confidence interval, 2.0 to 4.4), and delivery between 24 and 32 weeks of gestation (relative risk, 2.1; 95 percent confidence interval, 1.1 to 4.0), but not with delivery between 33 and 36 weeks (relative risk, 1.0; 95 percent confidence interval, 0.7 to 1.5).

Conclusions Suboptimal first-trimester growth may be associated with low birth weight, low birth-weight percentile, and premature delivery. (N Engl J Med 1998;339:1817-22.)

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LOW birth weight (less than 2500 g) and birth weight that is low for gestational age are associated with increased perinatal morbidity and mortality,¹ short- and long-term childhood morbidity and mortality,^{2,3} and a range of cardiovascular and metabolic diseases in later life.⁴ Consequently, the factors determining birth weight (other than gestational age) have been the focus of intense study for many years, and the risk factors for low birth weight at term have been reviewed in detail.⁵

It has previously been suggested that variations in fetal size are largely determined in the second half of

pregnancy.⁶ However, a 1993 study demonstrated a correlation between first-trimester crown-rump length and birth weight.⁷ We tested the hypothesis that a smaller-than-expected crown-rump length in the first trimester is associated with low birth weight and birth weight that is low for gestational age.

METHODS**Source of Data**

The results of all ultrasound scans obtained between 1985 and 1995 at the Queen Mother's Hospital, Glasgow, United Kingdom, were entered into a computer data base along with details of the women's medical, gynecologic, and obstetrical history, antenatal complications, and pregnancy outcome. The data base included all pregnant women referred for antenatal care, because all underwent ultrasonography at their first antenatal visit.

Over the 10-year period, 31,269 embryos or fetuses with a known date of delivery were scanned at least once. The gestational age at delivery was recorded for 31,259, and birth weight was recorded for 30,789. Of the 480 infants for whom birth weight was missing, 460 were delivered at less than 24 weeks.

We excluded pregnancies in which any of the following was present or had occurred: a history of rhesus isoimmunization (279 cases), essential hypertension (324 cases), cardiac disease (128 cases), type 1 diabetes mellitus (115 cases), other medical problems (992 cases), nonviable embryo or fetus at first scanning (115 cases), amniocentesis (1259 cases), chorionic-villus sampling (929 cases), multiple pregnancy (364 cases), antenatal detection of fetal abnormality (515 cases), therapeutic termination of pregnancy (224 cases), postnatal detection of fetal abnormality (560 cases), intrauterine contraceptive device seen on ultrasonography (42 cases), and second sac seen on ultrasonography (85 cases). There were a total of 4568 exclusions (some cases had multiple reasons for exclusion).

The crown-rump length was measured by the sonographer using electronic calipers on a frozen image on a monitor.⁸ The crown-rump length was converted to the equivalent number of days of gestational age on the basis of the following equation:

$$\text{gestational age in days} = 8.052 \sqrt{\text{crown-rump length in millimeters}} + 23.73.$$

The equation had been previously derived at the Queen Mother's Hospital with static ultrasonography⁹ and subsequently validated with real-time scanners (both transabdominal¹⁰ and transvaginal^{11,12}). It is currently recommended by the British Medical Ultrasound Society for first-trimester estimation of gestational age.⁸ The scans analyzed in the present study were obtained by real-time ultrasonography with several machines; the majority were transabdominal scans through a full urinary bladder.

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The inclusion criteria based on the ultrasonographic record were a single viable embryo or fetus present when the first ultrasound scan was obtained and a crown-rump length at the time of this scan that was less than the expected size in women who had had amenorrhea for 13 weeks. These criteria were fulfilled by 11,314 of the 26,701 nonexcluded cases.

The inclusion criteria from the menstrual history were that there was a date recorded for the first day of the last menstrual period and that it was recorded as certain, that the woman had not taken an oral contraceptive in the preceding 3 months, and that she had a regular 28-day menstrual cycle. Of the 11,314 women with no exclusion criteria who had an early ultrasound scan, 4229 fulfilled the menstrual inclusion criteria and had had their infants' birth weights recorded.

Analysis of the Data

The aim of the analysis was to relate first-trimester growth to the outcome of the pregnancy. The difference between the actual and predicted crown-rump length was expressed in days of gestation — that is, the estimated age in postmenstrual days according to crown-rump length minus the number of days of amenorrhea (i.e., the number of days since the beginning of the last menstrual period). A negative difference indicated an embryo (up to eight weeks of postconception age) or a fetus (after eight weeks of postconception age) that was smaller than expected. In pregnancies with a known date of conception through in vitro fertilization, the crown-rump length expressed in this way has 95 percent confidence intervals of approximately five to six days of postconception age in the first trimester.¹³ Therefore, our analysis focused on the 3397 embryos and fetuses in which the difference was between -6 and +6 days, because larger differences were unlikely to be due to variations in growth. Similarly, in the management of these pregnancies, the estimated gestational age was only altered on the basis of the crown-rump length when the difference was outside this range. Variation outside this range is presumably due to deviation of the time of ovulation from the assumed day 14 or to incorrect recollection of the menstrual history. A normal crown-rump length was defined as a value one day or less above or below the expected value (-1 to +1), because this is approximately equivalent to the standard deviation of repeated measurements in the first trimester.⁹

Low birth weight was defined as birth weight below 2500 g, and low birth weight at term was defined as birth weight below 2500 g at 37 or more weeks of gestation. Birth weight was also classified as above or below the fifth percentile for gestational age. Term was defined as at least 37 weeks of gestation, and preterm deliveries were subdivided into two groups — those at 24 to 32 weeks of gestation and those at 33 to 36 weeks of gestation.

Measurement of Maternal Serum Alpha-Fetoprotein

Maternal serum alpha-fetoprotein was measured between 15 and 20 weeks of gestation and quantified as multiples of the median for a given gestational age.¹⁴ These values were not corrected for maternal stature, since the data base contained only the analytical values.

Birth-Weight Percentiles

The birth-weight percentiles we used were derived from 120,250 live births in Scotland before 1985. A description of the collection and analysis of data on 55,387 live births between 1975 and 1979 has been published.¹⁵

Statistical Analysis

Numerical data were summarized as medians and interquartile ranges, and groups were compared with the Mann-Whitney U test. Proportions were compared with use of Fisher's exact test (two-tailed) and relative risks and 95 percent confidence intervals.

The effect of multiple variables on dichotomous outcomes was analyzed by logistic-regression analysis. Statistical analysis was performed with the Stata software package (release 5.0 for Windows NT, Stata, College Station, Tex.).

RESULTS

The distribution of the differences between the values for observed and expected crown-rump length was skewed toward negative values: the mode was 0 days, the median was -1 day, and the interquartile range was -4 to 0 days. When the comparison was made between embryos or fetuses that were smaller than expected, approximately as large as expected, and larger than expected, there were significant differences in the proportions of infants with low birth weight (<2500 g), low birth weight at term (<2500 g at 37 or more weeks), birth weight below the fifth percentile for gestational age, delivery between 24 and 32 weeks, and birth weight greater than 4000 g (Table 1). The association between smaller-than-expected crown-rump length and low birth weight was significant in pregnancies with values of -7 to -2 for the number of days of difference between observed and expected length (Fig. 1).

The proportions with these outcomes in the groups with larger-than-expected (+2 to +6 days) and normal (-1 to +1 day) crown-rump lengths were similar (Table 1). These two groups were therefore pooled to form the reference group. As compared with this group, embryos or fetuses with a smaller-than-expected crown-rump length (-6 to -2 days) had an increased risk of low birth weight, low birth weight at term, birth weight below the fifth percentile for gestational age, and delivery between 24 and 32 weeks, but not delivery between 33 and 36 weeks (Table 2). The associations were still significant when gestational age at delivery was calculated from the crown-rump length rather than from the last menstrual period (Table 2). The relative risks were of similar magnitude and statistical significance when the normal group (-1 to +1 day) was used as the reference group.

A smaller-than-expected crown-rump length was associated with an increase of borderline significance in the risk of an elevated maternal serum alpha-fetoprotein concentration in the second trimester (P=0.09) (Table 2). An elevated maternal serum alpha-fetoprotein concentration was significantly associated with low birth weight, low birth weight at term, and premature delivery among embryos or fetuses with smaller-than-expected crown-rump lengths (Table 3).

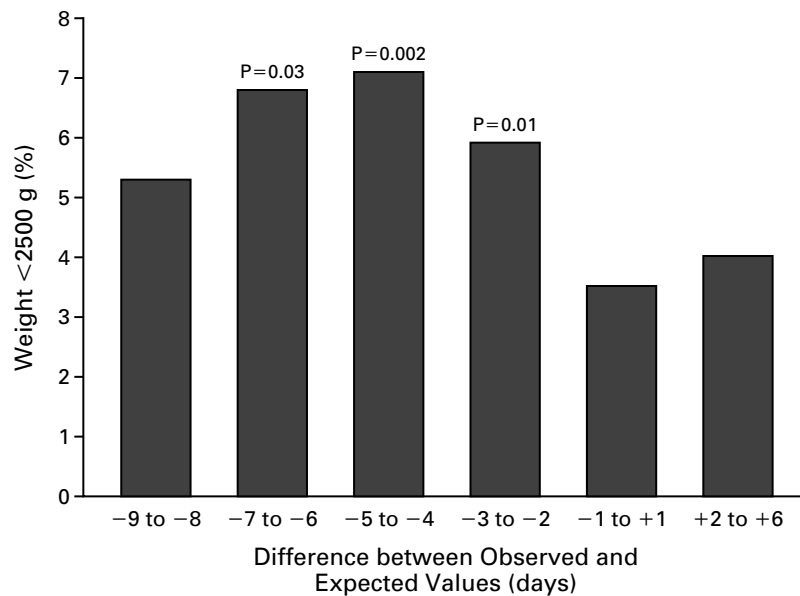
A smaller-than-expected crown-rump length was associated with several other potential risk factors for low birth weight (Table 4). Furthermore, the proportion of embryos or fetuses with smaller-than-expected crown-rump lengths was slightly higher

TABLE 1. ADVERSE OUTCOMES ACCORDING TO THE DIFFERENCE BETWEEN OBSERVED AND EXPECTED FIRST-TRIMESTER CROWN-RUMP LENGTHS.

OUTCOME	CROWN-RUMP LENGTH*			P VALUE†
	SMALLER THAN EXPECTED	NORMAL	LARGER THAN EXPECTED	
	% (no. with outcome/no. without outcome)			
Birth weight <2500 g	6.4 (83/1206)	3.5 (53/1461)	4.0 (24/570)	0.001
Birth weight <2500 g at ≥37 wk	2.9 (38/1251)	1.3 (20/1494)	1.2 (7/587)	0.004
Birth weight <5th percentile	5.0 (65/1224)	1.6 (24/1490)	2.0 (12/582)	<0.001
Birth weight >4000 g	9.2 (119/1170)	11.5 (174/1340)	12.8 (76/518)	0.04
Delivery at 24–32 wk	1.7 (22/1267)	0.7 (11/1503)	1.0 (6/587)	0.05
Delivery at 33–36 wk	3.9 (50/1239)	3.6 (55/1459)	3.9 (23/570)	0.93

*Crown-rump length was expressed as equivalent days of growth. Smaller than expected was -6 to -2 days, normal -1 to +1 day, and larger than expected +2 to +6 days.

†P values are for the comparison of proportions in the three groups by Fisher's exact test. Gestational age at delivery was calculated from the last menstrual period.



NO. OF INFANTS	-9 to -8	-7 to -6	-5 to -4	-3 to -2	-1 to +1	+2 to +6
Weight <2500 g	8	14	33	44	53	24
Weight ≥2500 g	142	191	429	705	1461	570

Figure 1. Proportion of Infants with Birth Weights of Less Than 2500 g According to the Difference between Observed and Expected First-Trimester Crown-Rump Lengths.

P values are for the comparison with the group with normal crown-rump length (-1 to +1 day) by Fisher's exact test (two-tailed). The proportion of infants with low birth weight in the pooled group for whom the difference was -9 to +6 days was not significantly different from the proportion of infants for whom the difference was less than -9 days (32 of 492; P=0.12) or greater than +6 days (2 of 63; P=0.77). The crown-rump length was expressed as equivalent days of growth.

TABLE 2. RELATIVE RISKS ASSOCIATED WITH A SMALLER-THAN-EXPECTED FIRST-TRIMESTER CROWN-RUMP LENGTH.

OUTCOME	CROWN-RUMP LENGTH*		RELATIVE RISK (95% CI)†	P VALUE‡
	SMALLER THAN EXPECTED	NORMAL OR LARGER THAN EXPECTED		
	no. with outcome/ no. without outcome			
Birth weight <2500 g	83/1206	77/2031	1.8 (1.3–2.4)	<0.001
Birth weight <2500 g at ≥37 wk according to last menstrual period	38/1251	27/2081	2.3 (1.4–3.8)	<0.001
Birth weight <2500 g at ≥37 wk according to crown-rump length	33/1256	26/2081	2.1 (1.2–3.5)	0.006
Birth weight <5th percentile according to last menstrual period	65/1224	36/2072	3.0 (2.0–4.4)	<0.001
Birth weight <5th percentile according to crown-rump length	45/1244	42/2066	1.8 (1.2–2.7)	0.01
Alpha-fetoprotein >2× median§	41/1050	44/1657	1.5 (1.0–2.2)	0.09
Emergency cesarean section	120/1169	204/1904	1.0 (0.8–1.2)	0.76
Perinatal death	3/1286	6/2102	0.8 (0.2–3.3)	1.0
Delivery at 24–32 wk according to last menstrual period	22/1267	17/2090	2.1 (1.1–4.0)	0.02
Delivery at 24–32 wk according to crown-rump length	23/1266	17/2091	2.2 (1.2–4.1)	0.01
Delivery at 33–36 wk according to last menstrual period	50/1239	78/2029	1.0 (0.7–1.5)	0.78

*Crown-rump length was expressed as equivalent days of growth. Smaller than expected was -6 to -2 days, and normal or larger than expected -1 to +6 days.

†CI denotes confidence interval.

‡P values are for the comparison between groups by a two-tailed Fisher's exact test.

§Testing of alpha-fetoprotein was optional; 82 percent of the patients elected to have the test performed.

TABLE 3. OCCURRENCE OF ADVERSE OUTCOMES ACCORDING TO MATERNAL SERUM ALPHA-FETOPROTEIN LEVEL AND THE DIFFERENCE BETWEEN OBSERVED AND EXPECTED CROWN-RUMP LENGTHS.*

OUTCOME	SMALLER-THAN-EXPECTED LENGTH				NORMAL OR LARGER-THAN-EXPECTED LENGTH			
	ELEVATED AFP	NORMAL AFP	RR (95% CI)	P VALUE†	ELEVATED AFP	NORMAL AFP	RR (95% CI)	P VALUE†
	no. with outcome/ no. without outcome				no. with outcome/ no. without outcome			
Birth weight <2500 g	8/33	58/992	3.5 (1.8–6.9)	0.002	2/42	64/1593	1.2 (0.3–4.7)	0.69
Birth weight <2500 g at ≥37 wk	4/37	24/1026	4.3 (1.6–11.7)	0.02	1/43	25/1632	1.5 (0.2–10.9)	0.50
Delivery at 24–32 wk	3/38	15/1035	5.1 (1.5–17.0)	0.03	1/43	13/1644	2.9 (0.4–21.7)	0.31

*AFP denotes maternal serum alpha-fetoprotein, RR relative risk, and CI confidence interval. Crown-rump length was expressed as equivalent days of growth. Smaller than expected was -6 to -2 days, and normal or larger than expected -1 to +6 days. An elevated alpha-fetoprotein level was defined as a level more than two times the median.

†P values are for the comparison between groups by a two-tailed Fisher's exact test.

for scans performed before the 10th week of amenorrhea than for scans performed later: 42 percent (261 of 622) as compared with 37 percent (1028 of 2775) (P=0.02). However, the relations between first-trimester growth and these outcomes were still significant in multivariate logistic-regression analyses that included a number of other risk factors and early ultrasound studies as covariates (Table 5).

DISCUSSION

The central findings of our study are that there is a significant relation between smaller-than-expected size in the first trimester and low birth weight (<2500 g), birth weight that is low for gestational age, and extremely premature delivery (24 to 32 weeks) among otherwise normal babies. Restricted growth of the embryo or fetus in very early preg-

TABLE 4. FREQUENCY OF POSSIBLE RISK FACTORS FOR LOW BIRTH WEIGHT AND LOW WEIGHT FOR GESTATIONAL AGE ACCORDING TO THE DIFFERENCE BETWEEN OBSERVED AND EXPECTED FIRST-TRIMESTER CROWN-RUMP LENGTHS.

RISK FACTOR	CROWN-RUMP LENGTH*		P VALUE†
	SMALLER THAN EXPECTED (N=1289)	NORMAL OR LARGER THAN EXPECTED (N=2108)	
	median (interquartile range)		
Mother's age (yr)	28 (25-31)	27 (24-30)	<0.001
Gestational age at time of ultrasound scan (days)			
According to last menstrual period	83 (72-89)	81 (73-86)	<0.001
According to crown-rump length	79 (74-87)	82 (74-87)	<0.001
Parity	1 (0-1)	1 (0-1)	0.17
No. of previous spontaneous abortions	0 (0-0)	0 (0-0)	0.77
No. of previous therapeutic abortions	0 (0-0)	0 (0-0)	0.74
	% (no.)		
Mother's age, <20 yr	5.2 (67)	3.3 (69)	0.007
Mother's age, >40 yr	0.0 (0)	0.2 (5)	0.16
Mother nulliparous	48.3 (622)	45.2 (952)	0.08
Parity >3	1.8 (23)	1.7 (36)	0.89
Bleeding			
1st trimester	10.9 (141)	9.0 (189)	0.06
2nd trimester	3.2 (41)	2.6 (55)	0.34
3rd trimester	5.2 (67)	4.6 (98)	0.51
Pregnancy-induced hypertension	10.9 (141)	11.1 (235)	0.87
Elective delivery	28.7 (370)	23.3 (491)	<0.001
Male infant	49.4 (637)	52.2 (1101)	0.11

*Crown-rump length was expressed as equivalent days of growth. Smaller than expected was -6 to -2 days, and normal or larger than expected -1 to +6 days.

†Medians were compared by the Mann-Whitney U test, and proportions by Fisher's exact test (two-tailed).

TABLE 5. ADJUSTED ODDS RATIOS FOR ADVERSE OUTCOMES ASSOCIATED WITH A SMALLER-THAN-EXPECTED CROWN-RUMP LENGTH.*

OUTCOME	ADJUSTED ODDS RATIO (95% CI)	P VALUE
Birth weight <2500 g	1.7 (1.2-2.3)	0.002
Birth weight <2500 g at ≥37 wk	2.1 (1.3-3.5)	0.004
Birth weight <5th percentile	2.8 (1.9-4.3)	<0.001
Delivery at 24-32 wk	2.0 (1.1-4.0)	0.03

*The logistic-regression models included age; parity; previous spontaneous abortions; previous therapeutic abortions; bleeding in the first, second, and third trimesters; pregnancy-induced hypertension; elective delivery; fetal sex; and ultrasound scanning before 10 weeks. The adjusted odds ratio associated with a smaller-than-expected crown-rump length (difference from expected, -6 to -2 days) is with reference to the pooled group with either normal crown-rump length (-1 to +1 day) or a larger-than-expected crown-rump length (+2 to +6 days). CI denotes confidence interval.

nancy may be causally related to these outcomes. However, given the highly selected nature of the pregnancies in which these measurements can be made, the proportion of these outcomes that might be attributed to first-trimester growth in the general population is not known.

In our study, unlike studies of conceptions by means of in vitro fertilization, the exact postconception age at the time of ultrasonography was unknown. The size of the embryo or fetus in the first trimester may also differ from the expected size because of variation in the timing of ovulation. If ovulation occurred on day 17 and was followed by normal conception, implantation, and growth, the fetus would be the equivalent of 3 days smaller than would be expected if ovulation had taken place on day 14. If this fetus was then born 41 weeks after the last menstrual period, gestational age would be the postconception equivalent of 40 weeks and 4 days, but the infant's birth weight would be judged by the 41-week percentile. However, the relations of a smaller-than-expected crown-rump length with low birth weight at term and birth weight below the fifth percentile were still significant when gestational age at delivery was calculated from the crown-rump length.

We found that the risk of low birth weight was lowest among embryos or fetuses with a normal or larger-than-expected crown-rump length (difference from expected of -1 to +6 days). The risk of low birth weight was increased when the difference between the observed and expected crown-rump length was -7 to -2 days. Outside this range, the risk of low birth weight was similar to the average for the whole group. We interpret this pattern to mean that when the differences between observed and expected crown-rump length are large, the measurement gives little information about the growth of the embryo or fetus, because large differences are most likely due to an incorrectly estimated postconception age that largely obscures the variation related to growth.^{7,13} Therefore, the risk of low birth weight is similar to the average. In groups with moderately negative values (-7 to -2 days), there is a greater proportion of cases in which the embryo or fetus is smaller than expected because of below-average growth, and therefore the risk of low birth weight is higher. However, as the difference between the observed and expected sizes nears zero and then becomes positive, the proportion of cases in which the growth of the embryo or fetus is suboptimal is smaller, and therefore the risk of low birth weight is lower.

The distribution of the difference between observed and expected crown-rump length was skewed toward negative values. This is unlikely to be due to an error in the equation used, since the mode of the difference was zero, and 36 percent of measurements were within ±1 day of the estimated value. The skewing is more likely to be due to a skewing

in the timing of ovulation toward the second half of the cycle.¹⁶ It may also be related to skewing in the distribution of embryonic or fetal size toward small stature.

The prediction of adverse outcome by a smaller-than-expected crown-rump length was additive with the predictive power of a high maternal serum alpha-fetoprotein concentration in the second trimester (Table 3). The apparent lack of a significant relation between maternal serum alpha-fetoprotein concentrations and adverse outcomes in cases involving normal or larger-than-expected crown-rump lengths may be due to the small number of adverse outcomes in this group.

If there is a causal relation between poor first-trimester growth and low birth weight, it may be that a suboptimal environment in the first trimester limits fetal growth for the remainder of pregnancy. Alternatively, poor growth in the first trimester may be secondary to a disorder of placentation that is manifested throughout pregnancy by suboptimal transfer of nutrients to the fetus. It also seems likely that some fetuses may be physiologically small throughout pregnancy.

The association between a smaller-than-expected crown-rump length and delivery between 24 and 32 weeks, but not between 33 and 36 weeks, is consistent with the hypothesis that the pathophysiology of extremely premature delivery may be different from that of moderately premature delivery.¹⁷ Furthermore, it suggests that in at least a proportion of cases, extremely premature delivery may be the result of a chronically suboptimal intrauterine environment, a possibility that is consistent with the results of other studies of the causes of premature delivery.¹⁸

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